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Vibrational spectroscopic studies on 2′-3′-didehydro-2′-3′-dideoxythymidine using density functional theory method

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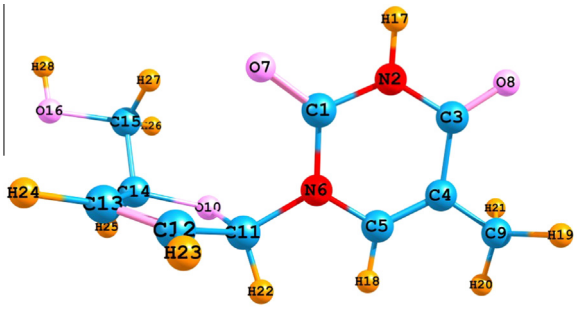
HIGHLIGHTS

- FT-IR, FT-Raman, Thermal analysis and UV–vis spectra of 2′-3′-didehydro-2′-3′-dideoxythymidine in the solid phase were recorded and analyzed.
- The optimized geometry and vibrational wavenumbers were computed using DFT(B3LYP) methods.
- Selected vibrational assignment and spectroscopic analysis have been carried out.
- Natural atomic analysis explained the intramolecular hydrogen bonding.
- Chemical shift of the title compound were found.

GRAPHICAL ABSTRACT

Anti-HIV agent of 2′-3′-didehydro-2′-3′-dideoxythymidine has been studied along with its structure in this article using the theoretical and experimental values based on various methods.



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ABSTRACT

FTIR and FT-Raman spectra of 2′-3′-didehydro-2′-3′-dideoxythymidine have been recorded and analyzed. The molecular geometry and vibrational frequencies and intensity of the vibrational bands are interpreted with the aid of structure optimization based on density functional theory (DFT) B3LYP method with 6-31G(d,p) and 6-31++G(d,p) basis sets. The results of the optimized molecular structure are presented and compared with the experimental X-ray diffraction data. The theoretical results show that the optimized geometry can well reproduce the crystal structure, and the calculated vibrational frequency values show good agreement with experimental values. A study of the electronic properties, such as HOMO and LUMO energies were performed. Mulliken charges and NBO charges of the title molecule were also calculated and interpreted. Thermogravimetric analysis has been done to study the thermal behavior of 2′-3′-didehydro-2′-3′-dideoxythymidine. The ^{13}C nuclear magnetic resonance (NMR) chemical shift of the molecule are calculated by the gauge independent atomic orbital (GIAO) method and compared with experimental results.

1. Introduction

2′-3′-Didehydro-2′-3′-dideoxythymidine is a nucleotide reverse transcriptase inhibitor, used in the treatment of infection by retrovirus, primarily HIV. It is chemically known as [1-((2R,5S)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione]. 2′-3′-didehydro-2′-3′-dideoxythymidine has absorbed 80% approximately from the gastrointestinal tract and undergoes considerable first-pass metabolism [1]. As it has short biological half-life 0.8–1.5 h and low daily dose of 30 mg, 2′-3′-didehydro-2′-3′-dideoxythymidine should be formulated in a

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sustained release dosage form to improve patient compliance. Microencapsulation is a process whereby one can formulate controlled/sustained action dose form of drugs having a short half-life [2]. Microencapsulation drug absorption minimizes side effects which are due to the localized buildup of drugs against the gastrointestinal mucosa [3].

To our knowledge, density functional theory (DFT) calculations on detailed vibrational infrared (IR) and Raman analysis have not been performed on the title molecule. A detailed quantum chemical investigation will be helpful in understanding the vibrational modes of 2′-3′-didehydro-2′-3′-dideoxythymidine and thus clarifying the experimental data available for this molecule. DFT calculations are known to provide excellent vibrational wavenumbers scaled to compensate for the approximate treatment of electron correlation, for basis set deficiencies and anharmonicity effects [4–9]. In this work, by using DFT-B3LYP methods with two different basis sets, we calculated the vibrational wavenumbers of 2′-3′-didehydro-2′-3′-dideoxythymidine and molecular geometric parameters. These calculations are valuable for providing insight into the vibrational spectrum and molecular parameters. DFT is the best method rather than the ab initio method for the computation of molecular structure, vibrational wavenumbers and energies of molecules [10].

2. Experimental detail

The FTIR spectrum was recorded using Nexus 670 DTGS FT-IR spectrometer in the region 4000–400 cm^{-1} at room temperature using KBr pellet technique and each IR spectrum was acquired in 10 scans at 4 cm^{-1} resolution. The band intensities were expressed in transmittance (%). Raman spectral measurements were made with Nexus 670 spectrometer. An air cooled diode pumped Nd: YAG laser, operated at 1064 nm and a power output of 100 mW was used as a source. The spectra were traced in the range 4000–100 cm^{-1} with 500 scans at 4 cm^{-1} resolution. Both infrared and Raman analysis permitted the identification of the main molecular groups present in the sample.

Thermal analysis was performed in a simultaneous TG–DTA instrument (SDT Q 6000 V 8.2 Built 100 thermal analyzer). The experimental conditions were: (i) continuous heating from room temperature to 1000 °C at a heating rate of 20 °C/min, (ii) air atmosphere, (iii) alumina, as reference material and (iv) sample: 5.00 mg of the sample without pressing. The temperature was detected with a Pt–Pt 13% Rh thermocouple fixed in a position near the sample pan.

3. Computational method

All the theoretical computations were performed at DFT-B3LYP levels on a Pentium IV/1.6 GHz personal computer using the Gaussian 03W program package [11]. The geometries were optimized at the DFT level of theory employing the 6-31G(d,p) and 6-31++G(d,p) basis sets. The DFT method employed the B3LYP keyword, which invokes Becke's three-parameter hybrid method [10] using the correlation function of Lee et al. [12]. Polarization functions were added for the better description of polar bonds of amino and nitro groups. The optimized geometry was used in the vibrational frequency calculations at DFT levels to characterize all the stationary points as minima. The vibrational frequency assignments were made with a high degree of accuracy with the help of the Chemcraft software program (Chem3D Ultra 8.0, Cambridge soft. com, Cambridge, MA, USA).

4. Results and discussion

4.1. Molecular geometry

The optimized molecular structure of 2′-3′-didehydro-2′-3′-dideoxythymidine in the ground state was computed by B3LYP

Table 1
Selected Comparison between the two basis sets of DFT method of geometrical parameters of 2′-3′-didehydro-2′-3′-dideoxythymidine.

Bond length (Å)				Bond angle (deg)			
Parameters	B3LYP/6-31G(d,p)	B3LYP/6-31++G(d,p)	Ref. [13]	Parameters	B3LYP/6-31G(d,p)	B3LYP/6-31++G(d,p)	Ref. [13]
C1—O7	1.219	1.222	1.208	N2—C1—O7	122.1	122.0	121.8
N2—H17	1.013	1.014	1.012	N2—C3—C4	113.6	114.0	114.9
C3—O8	1.222	1.226	1.208	N2—C3—O8	121.7	121.4	122.6
C4—C5	1.351	1.353	1.338	C3—C4—C9	118.0	118.5	119.3
C4—C9	1.501	1.502	1.497	C4—C5—H18	121.0	120.9	119.5
C5—N6	1.387	1.388	1.369	C1—N6—C5	120.7	120.6	118.5
C5—H18	1.085	1.085	1.100	C1—N6—C11	120.2	120.5	120.7
N6—C11	1.480	1.480	1.450	C5—N6—C11	118.8	120.6	120.7
C9—H19	1.095	1.095	1.113	C4—C9—H19	110.8	110.9	109.5
C9—H20	1.093	1.094	1.113	C4—C9—H20	111.3	111.1	109.4
C9—H21	1.095	1.095	1.113	C4—C9—H21	110.8	110.9	109.5
O10—C11	1.414	1.417	1.402	H19—C9—H20	108.6	108.6	109.4
O10—C14	1.442	1.445	1.456	H20—C9—H21	108.6	108.6	109.5
C11—C12	1.507	1.507	1.497	C11—O10—C14	110.4	110.5	112.5
C11—H22	1.100	1.099	1.113	N6—C11—O10	111.3	111.2	110.8
C12—C13	1.328	1.330	1.337	N6—C11—C12	110.1	110.5	110.8
C12—H23	1.083	1.083	1.100	O10—C11—C12	105.5	105.3	104.0
C13—C14	1.502	1.503	1.497	O10—C11—H22	111.4	111.0	112.6
C13—H24	1.082	1.083	1.100	C12—C11—H22	111.2	111.2	112.6
C14—C15	1.530	1.530	1.523	C11—C12—H23	123.6	122.6	124.5
C14—H25	1.100	1.099	1.113	C12—C13—C14	110.0	110.2	111.0
C15—O16	1.425	1.412	1.402	C14—C13—H24	123.4	122.5	124.5
C15—H26	1.101	1.099	1.113	O10—C14—C15	110.8	109.5	111.4
C15—H27	1.096	1.095	1.113	C13—C14—C15	114.3	111.6	111.4
O16—H28	0.965	0.955	0.942	C14—C15—H26	108.5	108.5	109.4
				C14—C15—H27	108.8	109.4	109.5
				O16—C15—H26	111.8	111.1	109.4
				H26—C15—H27	108.7	109.3	109.5
R^2	0.9944	0.9953		R^2	0.9380	0.9531	